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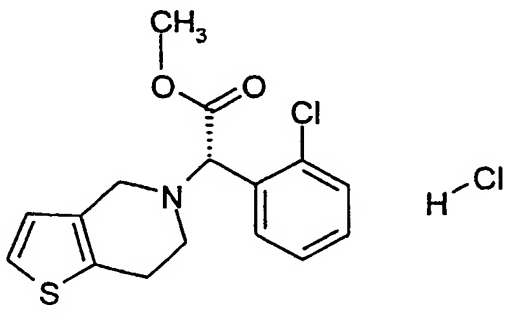

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(57) Abstract: The invention relates to crystalline forms I and II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2.c]pyridine-5-yl)-acetate hydrochloride of the Formula (I) and hydrates thereof, a process for the preparation thereof and pharmaceutical compositions containing the same. The new polymorphs according to the invention exhibit blood platelet aggregation inhibiting and antithrombotic effect.

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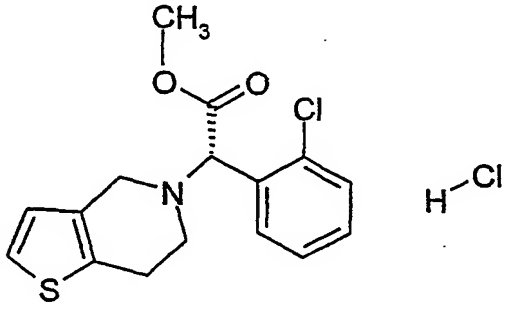
POLYMORPHS OF CLOPIDOGREL HYDROCHLORIDE AND THEIR USE AS ANTITHROMBIC COMPOUNDS

FIELD OF THE INVENTION

This invention relates to new polymorphs of clopidogrel hydrochloride, a process for the preparation thereof, pharmaceutical compositions comprising said new polymorphs and the use of the new polymorphs for blood platelet aggregation inhibiting and antithrombotic treatment.

More particularly the invention is concerned with new crystalline forms I and II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula



(I)

and hydrates thereof, a process for the preparation of the new polymorphs, pharmaceutical compositions comprising said new

polymorphs and the use of the new polymorphs for blood platelet aggregation inhibiting and antithrombotic treatment.

TECHNICAL BACKGROUND

Methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrogen sulfate is a known blood platelet aggregation inhibitory and antithrombotic pharmaceutical active ingredient having the INN (International Non-Proprietory Name) clopidogrel hydrogen sulfate.

Clopidogrel hydrogen sulfate was first described in EP 281,459 corresponding to HU 197,909. Methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride was also first disclosed in this patent specification. According to said patent the hydrochloride salt is prepared by dissolving clopidogrel base in diethyl ether and precipitating the salt with diethyl ether containing hydrogen chloride. In the patent specification methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride is characterized by its melting point of 117°C and optical rotation of $[\alpha]_D^{20} = +62.23°$ (c=1.82, methanol). The patent is, however, completely silent in disclosing the crystal form of the product and IR or X-ray

powder diffraction data characterizing the crystalline form are not described either.

According to HU 215,957 methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride is prepared in a similar way by dissolving clopidogrel base in diethyl ether and precipitating the salt with diethyl ether containing hydrogen chloride. In the patent the product is characterized by a protracted melting point interval of 130-140°C and an optical rotation of $[\alpha]_D^{20} = +63°$ (c=1, methanol). There is no teaching of the crystal form of the product and IR or X-ray powder diffraction data characteristic of the product are not disclosed either.

According to WO 98/51681, WO 98/51682, WO 98/51689 and WO 2000/27840 methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride is prepared by dissolving methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate base in diethyl ether, introducing anhydrous gaseous hydrogen chloride into the solution and isolating the crystals formed by filtration. The hydrogen chloride salt is characterized by a melting point of 130-132°C and an optical rotation of $[\alpha]_D^{20} = +60°$. There is no disclosure of the crystal form of the product, and the IR or X-

ray powder diffraction data characteristic of the product are not mentioned either.

Thus clopidogrel hydrochloride of uniform crystal form has not been described in prior art. On the other hand there is a strong need in pharmaceutical industry for active ingredients of uniform morphology. It is known that various polymorphs differ from each other significantly in their important properties (e.g. dissolution speed, bioavailability, chemical stability). Also from a technological point of view there is a strong need for morphologically uniform pharmaceutical active ingredients which can be produced in a reproducible manner on industrial scale too, because the working-up and processing properties of the various polymorphs (e.g. filtrability, drying, solubility, readiness to be compressed into tablets) differ from each other significantly.

SUMMARY OF THE INVENTION

It is the object of the present invention to provide clopidogrel hydrochloride polymers having uniform morphology meeting the above requirements which can be manufactured in a reproducible manner on industrial scale too.

The above object is solved by the new crystalline methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride polymorphs of the present invention.

The present invention is based on the surprising recognition that two new uniform crystalline forms of clopidogrel hydrochloride can be prepared in a reproducible manner as described below. The melting point of the new polymorphs of the present invention is significantly different from that of the data disclosed in prior art.

According to the present invention there is provided new crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula I and hydrates thereof characterized by the X-ray powder diffraction pattern expressed in Table 1 and Figure 1.

Table 1

Position of diffraction lines and relative intensities

(> 15 % of polymorph I)

Peak No.	2*th [deg]	D(hkl) [Ĺ]	I(abs) [cts]	I(rel) [%]	Peak No.	2*th [deg]	D(hkl) [Ĺ]	I(abs) [cts]	I(rel) [%]
1	9.64	9.1707	152	21.51	12	21.64	4.1075	107	15.16
2	11.22	7.8873	129	18.25	13	22.90	3.8841	476	67.21

Peak No.	2*th [deg]	D(hkl) [Ĺ]	I(abs) [cts]	I(rel) [%]	Peak No.	2*th [deg]	D(hkl) [Ĺ]	I(abs) [cts]	I(rel) [%]
3	12.98	6.8222	708	100	14	23.13	3.8455	469	66.30
4	13.89	6.3759	161	22.76	15	24.73	3.6006	245	34.67
5	15.05	5.8888	115	16.25	16	25.06	3.5540	302	42.62
6	16.82	5.2697	168	23.66	17	25.41	3.5059	471	66.49
7	17.16	5.1661	189	26.76	18	27.31	3.2655	111	15.73
8	17.65	5.0261	156	22.06	19	27.55	3.2372	179	25.25
9	19.58	4.5336	193	27.33	20	28.78	3.1021	143	20.16
10	19.88	4.4654	393	55.56	21	28.97	3.0822	123	17.39
11	20.57	4.3180	165	23.37	22	32.48	2.7570	190	26.77

According to the present invention there is also provided new crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula I and hydrates thereof characterized by the X-ray powder diffraction pattern expressed in Table 2 and Figure 2.

Table 2

Position of diffraction lines and relative intensities

(> 15 % of polymorph I)

Peak No.	2*th [deg]	D(hkl) [Ĺ]	I(abs) [cts]	I(rel) [%]	Peak No.	2*th [deg]	D(hkl) [Ĺ]	I(abs) [cts]	I(rel) [%]
1	8.85	9.9923	88	15.83	19	22.25	3.9956	184	33.09
2	9.85	8.9800	535	96.22	20	22.58	3.9386	156	28.06
3	11.41	7.7575	358	64.39	21	22.85	3.8920	134	24.10
4	12.97	6.8260	101	18.17	22	23.26	3.8250	523	94.06
5	13.49	6.5640	123	22.12	23	23.80	3.7386	443	79.68
Peak	2*th	D(hkl)	I(abs)	I(rel)	Peak	2*th	D(hkl)	I(abs)	I(rel)

No.	[deg]	[Ĺ]	[cts]	[%]	No.	[deg]	[Ĺ]	[cts]	[%]
6	16.31	5.4362	248	44.60	24	24.21	3.6759	173	31.12
7	16.73	5.2988	182	32.73	25	26.10	3.4143	260	46.76
8	17.01	5.2128	142	25.54	26	26.62	3.3491	388	69.78
9	17.69	5.0139	446	80.22	27	27.14	3.2862	238	42.81
10	17.85	4.9693	556	100	28	27.72	3.2189	350	62.95
11	18.09	4.9039	403	72.48	29	28.09	3.1768	113	20.32
12	18.44	4.8103	123	22.12	30	28.67	3.1141	369	66.37
13	19.53	4.5455	363	65.29	31	29.21	3.0573	123	22.12
14	19.93	4.4547	482	86.69	32	29.54	3.0237	155	27.88
15	20.46	4.3407	140	25.18	33	31.42	2.8475	148	26.62
16	20.92	4.2457	365	65.65	34	32.54	2.7515	117	21.04
17	21.33	4.1662	232	41.73	35	34.13	2.6270	180	32.37
18	21.92	4.0546	401	72.12					

DETAILED DESCRIPTION OF THE INVENTION

The powder diffraction pattern of new crystalline polymorph I is determined under the following conditions:

Equipment: PHILIPS – XPERT PW 3710 powder diffractometer

Radiation: CuKα (λ: 1.54190Ĺ)

Monochromator: graphite

Exciting voltage: 40 kV

Anode current: 30 Ma

Method:

Standard reference substance: SRM 675

Mica Powder (synthetic fluorographite), Ser. No.: 981307.

The measurement is continuous: Θ/2Θ scan: 4.5° – 35.00° 2Θ
Step size: 0.04°
Sample: surface plain, width 0.5 mm, in quartz sample holder, measured and stored at room temperature.

According to the present invention there is also provided a process for the preparation of crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula I and hydrates thereof which comprises

a) dissolving methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate in a dipolar aprotic solvent, or in a less polar aprotic solvent, or in a polar solvent or in a mixture thereof, admixing the solution with a solution of hydrogen chloride formed with a dipolar aprotic solvent, or a less polar aprotic solvent, or a polar solvent or a mixture thereof and isolating the crystalline form I polymorph; or

b) recrystallizing methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride from a dipolar aprotic solvent, or a less polar aprotic solvent or a mixture thereof.

As dipolar aprotic solvent preferably acetone, acetonitrile, ethyl acetate, or dimethyl formamide or a mixture thereof can be used.

As less polar aprotic solvent preferably dioxane, tetrahydrofurane, diisopropyl ether or a mixture thereof can be used.

As polar solvent preferably lower aliphatic alcohols (e.g. ethanol, n-propanol or 2-propanol) can be used.

According to process a) as solvent particularly advantageously acetone or ethyl acetate or a mixture of acetone and ethyl acetate can be used.

According to process b) as solvent particularly advantageously a mixture of acetone and ethyl acetate can be used.

Process a) can be preferably carried out by dissolving methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate base in one of the above solvents and thereafter admixing the solution with a solution of hydrogen chloride formed with one of the above solvents. Salt formation is preferably carried out at room temperature, whereupon the

mixture is cooled. The precipitated crystalline form I polymorph is isolated by filtration or centrifuging, washed and dried.

Process b) can be carried out by recrystallizing methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride from a dipolar aprotic solvent or a less polar aprotic solvent or a mixture thereof. As starting material methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride morphologically non-uniform or amorphous or having crystalline form II can be used. The dissolving of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride can be carried out under heating, preferably at the boiling point of the reaction mixture. The mixture is filtered, the filtrate cooled to a temperature of about room temperature or allowed to cool. The precipitation of crystals can be optionally promoted by inoculating with a small amount of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride crystals of crystalline form I. One may proceed advantageously by heating the solution of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride to the boiling point, cooling the solution first to room temperature and thereafter to a temperature between -20°C and +15°C, isolating the

precipitated crystals by filtration or centrifuging, washing and drying.

According to a further aspect of the present invention there is provided a process for the preparation of crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula I and hydrates thereof which comprises dissolving methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate in a dipolar aprotic solvent or a mixture thereof, admixing the solution with a solution of hydrogen chloride formed with an aprotic solvent or a mixture thereof and isolating the crystalline form II polymorph.

As dipolar aprotic solvent preferably acetone, acetonitrile, ethyl acetate or dimethyl formamide or a mixture thereof can be used.

One may proceed particularly advantageously by carrying out the process in a mixture of acetone and ethyl acetate.

According to a preferable form of realization of the process methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate is dissolved in a dipolar aprotic solvent or a mixture thereof, whereupon a solution of hydrogen chloride formed with a dipolar aprotic solvent or a mixture thereof is

added. One may proceed particularly advantageously by dissolving methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate base in a mixture of acetone and ethyl acetate and adding ethyl acetate containing hydrogen chloride. Salt formation is carried out preferably at room temperature. The precipitated crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride is isolated by filtration or centrifuging, washed and dried.

According to a still further aspect of the present invention there is provided a pharmaceutical composition comprising as active ingredient crystalline form I or II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula I or a hydrate thereof in admixture with inert solid or liquid pharmaceutical carriers and/or auxiliary agents.

The pharmaceutical compositions according to the present invention can be administered preferably orally or parenterally. The oral compositions may be e.g. tablets, capsules, dragées, solutions, elixirs, suspensions or emulsions. The parenteral pharmaceutical compositions can be preferably intravenous or intramuscular injections.

The pharmaceutical compositions can contain conventional pharmaceutical carriers and/or auxiliary agents. For this purpose e.g. magnesium carbonate, magnesium stearate, talc, lactose, pectine, dextrine, starch, gelatine, tragacanth, methyl cellulose, sodium carboxy methyl cellulose, lower melting wax, cocoa butter etc. can be used. Soft gelatine capsule can be often prepared without carrier - depending on the properties of the active ingredient – because the wall of the capsule can function as carrier. The oral compositions may be generally tablets, powders, capsules, pilules, cachets and losenges.

The suppositories contain as carrier e.g. lower melting waxes (e.g. mixtures of fatty acid glycerides or cocoa butter). Suppositories can be prepared by melting the wax and homogenously distributing the active ingredient in the melt wax. The thus obtained melted mixture is poured into moulds of suitable form and size and allowed to solidify under cooling.

The tablets can be prepared by admixing the active ingredient with suitable carriers and pressing the mixture into tablets of suitable form and size.

The powders can be prepared by admixing the finely powdered active ingredient with the finely powdered carrier.

The liquid compositions can be solutions, suspensions or emulsions from which the active ingredient can also be released in a sustained manner. The aqueous or aqueous-propylene glycol solutions are advantageous. The liquid pharmaceutical compositions suitable for parenteral administration can be preferably prepared in the form of an aqueous polyethylene glycol solution.

The aqueous solutions suitable for oral administration can be prepared by dissolving the active ingredient in water, optionally with the addition of suitable stabilizers, thickening agents, colourants and sweeteners.

Aqueous suspensions suitable for oral administration can be prepared by suspending the active ingredient in the presence of a viscous substance (e.g. natural or artificial gums, resins, methyl cellulose, sodium carboxy methyl cellulose or other suspending agents) in water.

Another type of solid pharmaceutical compositions is converted into a liquid formulation immediately before use and is administered orally as a liquid. The liquid compositions can be solutions, suspensions or emulsions which can optionally contain stabilizers, buffers, colourants, natural or artificial sweeteners, dispersing agents, thickening agents etc.

The pharmaceutical compositions according to the present invention can be preferably prepared in the form of dosage units which contain the desired amount of the active ingredient. Dosage units can be put on the market in packaged form which contain suitable separated amounts of the active ingredient (e.g. tablets or capsules in packages or vials, or powders in ampoules). The term "dosage unit" encompasses capsules, tablets, losenges and also the packaging which contains the suitable number of dosage units.

According to a further aspect of the present invention there is provided a process for the preparation of pharmaceutical compositions which comprises admixing crystalline form I or II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof with pharmaceutically acceptable solid or liquid carriers and/or auxiliary agents and bringing the mixture to a galenic form.

The pharmaceutical compositions according to the present invention are prepared by methods of pharmaceutical industry known *per se*.

The pharmaceutical compositions according to the present invention may contain in addition to crystalline form I or II

methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof further compatible pharmaceutical active ingredients.

The daily dose of crystalline form I or II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride depends on the circumstances of the given case (e.g. the condition and body weight of the patient, the severeness of the condition to be treated, the mode of administration etc.) and is determined by the physician.

According to a further aspect of the present invention there is provided the use of cystalline form I or II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof as pharmaceutical active ingredient.

According to a still further aspect of the present invention there is provided the use of crystalline form I or II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof as pharmaceutical active ingredient having blood platelet aggregation inhibiting and antithrombotic effect.

According to a still further aspect of the invention there is provided a blood platelet aggregation inhibiting and antithrombotic method of treatment which comprises administering to the patient in need of such treatment a therapeutically effective amount of crystalline form I or II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof.

The advantage of the present invention is that the new methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride polymorphs are of uniform morphology and therefore possess reproducible properties in relation to dissolution velocity, bioavailability, chemical stability, working-up and processing (filtrability, drying, tabletting properties etc.). The new polymorphs of the present invention can be prepared by a process which is readily reproducible on industrial scale too.

Further details of the present invention are to be found in the following Examples without limiting the scope of protection to said Examples.

Example 1

Preparation of crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride

3,21 g of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate are dissolved in 35 ml of tetrahydrofurane whereupon a solution of tetrahydrofurane saturated with gaseous hydrogen chloride is added. The reaction mixture is stirred at room temperature for 2 hours and thereafter allowed to stand in a refrigerator for 16 hours. The precipitated snow-white crystals are filtered off and washed with cold tetrahydrofurane. Thus 2.6 g of the title compound are obtained. Yield 75 %. Mp.: 140-141°C.

Example 2

Preparation of crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride

3.21 g of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate are dissolved in a mixture of 4 ml of acetone and 5 ml of ethyl acetate, whereupon 1.3 g of 2-propanol containing hydrogen chloride (31 g HCl/100 g solution) are added. The reaction mixture is stirred at room

temperature for 2 hours and thereafter allowed to stand in a refrigerator for 16 hours. The precipitated snow-white crystals are filtered off and washed with cold ethyl acetate. Thus 2.92 g of the title a compound are obtained. Yield 85 %. Mp.: 140-141°C.

Example 3

Preparation of crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride

3.21 g of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate are dissolved in 20 ml of ethyl acetate, whereupon 2.5 g of ethyl acetate containing hydrogen chloride are added (14 g HCl/100 g solution). The reaction mixture is stirred at room temperature for 2 hours and thereafter allowed to stand in a refrigerator for 16 hours. The precipitated snow-white crystals are filtered off and washed with cold tetrahydrofurane. Thus 2.92 g of the title compound are obtained. Yield 85 %. Mp.: 140-141°C.

Example 4

Preparation of crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride

3 g of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride are dissolved in 40 ml of boiling tetrahydrofurane. The hot solution is filtered, cooled slowly to room temperature under stirring, then stirred at room temperature for 2 hours and allowed to stand in a refrigerator for 16 hours. The precipitated snow-white crystals are filtered off and washed with cold tetrahydrofurane. Thus 2.5 g of the title compound are obtained. Yield 70 %. Mp.: 140-141°C.

Example 5

Preparation of crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride

3 g of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride are dissolved in a boiling mixture of 70 ml of acetone and 30 ml of diisopropyl ether. The hot solution is filtered, cooled slowly to room temperature under stirring, then stirred at room temperature for 2 hours and allowed to stand in a refrigerator for 16 hours. The precipitated snow-white crystals are filtered off and washed with cold ethyl acetate. Thus 2.2 g of the title compound are obtained. Yield 65 %. Mp.: 140-141°C.

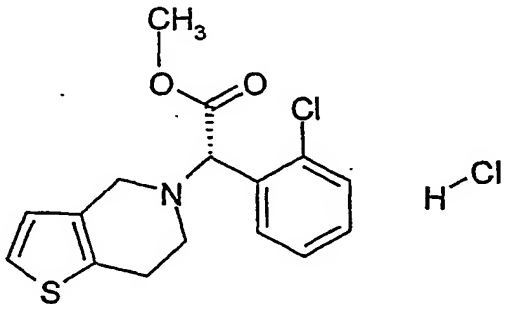
Example 6

Preparation of crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride

3.21 g of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate are dissolved at room temperature in a mixture of 10 ml acetone and 10 ml of ethyl acetate, whereupon 2.5 g of ethyl acetate containing hydrogen chloride (14 g HCl/100 g solution) are added. The reaction mixture is stirred at room temperature for 16 hours. The precipitated snow-white crystals are filtered off and washed with cold ethyl acetate. Thus 2.2 g of the title compound are obtained. Yield 64 %. Mp.: 143-144°C.

What we claim is,

1. Crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula



(I)

and hydrates thereof characterized by the X-ray powder diffraction pattern expressed in Table 1 and Figure 1.

Table 1

Position of diffraction lines and relative intensities

(> 15 % of polymorph I)

Peak No.	2*th [deg]	D(hkl) [Ĺ]	I(abs) [cts]	I(rel) [%]	Peak No.	2*th [deg]	D(hkl) [Ĺ]	I(abs) [cts]	I(rel) [%]
1	9.64	9.1707	152	21.51	12	21.64	4.1075	107	15.16
2	11.22	7.8873	129	18.25	13	22.90	3.8841	476	67.21
3	12.98	6.8222	708	100	14	23.13	3.8455	469	66.30
4	13.89	6.3759	161	22.76	15	24.73	3.6006	245	34.67

Peak No.	2*th [deg]	D(hkl) [Å]	I(abs) [cts]	I(rel) [%]	Peak No.	2*th [deg]	D(hkl) [Å]	I(abs) [cts]	I(rel) [%]
5	15.05	5.8888	115	16.25	16	25.06	3.5540	302	42.62
6	16.82	5.2697	168	23.66	17	25.41	3.5059	471	66.49
7	17.16	5.1661	189	26.76	18	27.31	3.2655	111	15.73
8	17.65	5.0261	156	22.06	19	27.55	3.2372	179	25.25
9	19.58	4.5336	193	27.33	20	28.78	3.1021	143	20.16
10	19.88	4.4654	393	55.56	21	28.97	3.0822	123	17.39
11	20.57	4.3180	165	23.37	22	32.48	2.7570	190	26.77

2. Process for the preparation of crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula I and hydrates thereof which comprises

a) dissolving methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate in a dipolar aprotic solvent, or in a less polar aprotic solvent, or in a polar solvent or in a mixture thereof, admixing the solution with a solution of hydrogen chloride formed with a dipolar aprotic solvent, or a less polar aprotic solvent, or a polar solvent or a mixture thereof and isolating the crystalline form I polymorph; or

b) recrystallizing methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride from a dipolar aprotic solvent, or a less polar aprotic solvent or a mixture thereof.

3. Process according to method a) or b) of Claim 2 which comprises using acetone, acetonitrile, ethyl acetate or dimethyl formamide or a mixture thereof as dipolar aprotic solvent.

4. Process according to method a) or b) of Claim 2 which comprises using dioxane, tetrahydrofurane, or diisopropyl ether or a mixture thereof as less polar aprotic solvent.

5. Process according to method a) of Claim 2 which comprises using a lower aliphatic alcohol, preferably ethanol, n-propanol or 2-propanol as polar solvent.

6. Process according to method a) of Claim 2 which comprises using as solvent acetone and/or ethyl acetate.

7. Process according to method b) of Claim 2 which comprises using a mixture of acetone and ethyl acetate as solvent.

8. Process according to method a) of Claim 2 or Claim 6 which comprises carrying out salt formation at room temperature and thereafter cooling the reaction mixture.

9. Process according to method b) of Claim 2 which comprises carrying out recrystallization by heating the solution of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride and thereafter cooling the solution.

10. Process according to Claim 9 which comprises heating the solution of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride to the boiling point of the solvent, then cooling to room temperature and thereafter cooling to a temperature between -20°C and +15°C.

11. Pharmaceutical composition comprising as active ingredient crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula I or a hydrate thereof in admixture with inert solid or liquid pharmaceutical carriers and/or auxiliary agents.

12. Process for the preparation of pharmaceutical compositions according to Claim 11 which comprises admixing crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof with pharmaceutically acceptable solid or

liquid carriers and/or auxiliary agents and bringing the mixture to a galenic form.

13. Crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof for use as pharmaceutical active ingredient.

14. Use of crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof as pharmaceutical active ingredient having blood platelet aggregation inhibiting and antithrombotic effect.

15. Blood platelet aggregation inhibiting and antithrombotic method of treatment which comprises administering to the patient in need of such treatment a therapeutically effective amount of crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof.

16. Crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula I and hydrates thereof

characterized by the X-ray powder diffraction pattern expressed in Table 2 and Figure 2.

Table 2

Position of diffraction lines and relative intensities

(> 15 % of polymorph I)

Peak No.	2*th [deg]	D(hkl) [Ĺ]	I(abs) [cts]	I(rel) [%]	Peak No.	2*th [deg]	D(hkl) [Ĺ]	I(abs) [cts]	I(rel) [%]
1	8.85	9.9923	88	15.83	19	22.25	3.9956	184	33.09
2	9.85	8.9800	535	96.22	20	22.58	3.9386	156	28.06
3	11.41	7.7575	358	64.39	21	22.85	3.8920	134	24.10
4	12.97	6.8260	101	18.17	22	23.26	3.8250	523	94.06
5	13.49	6.5640	123	22.12	23	23.80	3.7386	443	79.68
6	16.31	5.4362	248	44.60	24	24.21	3.6759	173	31.12
7	16.73	5.2988	182	32.73	25	26.10	3.4143	260	46.76
8	17.01	5.2128	142	25.54	26	26.62	3.3491	388	69.78
9	17.69	5.0139	446	80.22	27	27.14	3.2862	238	42.81
10	17.85	4.9693	556	100	28	27.72	3.2189	350	62.95
11	18.09	4.9039	403	72.48	29	28.09	3.1768	113	20.32
12	18.44	4.8103	123	22.12	30	28.67	3.1141	369	66.37
13	19.53	4.5455	363	65.29	31	29.21	3.0573	123	22.12
14	19.93	4.4547	482	86.69	32	29.54	3.0237	155	27.88
15	20.46	4.3407	140	25.18	33	31.42	2.8475	148	26.62
16	20.92	4.2457	365	65.65	34	32.54	2.7515	117	21.04
17	21.33	4.1662	232	41.73	35	34.13	2.6270	180	32.37
18	21.92	4.0546	401	72.12					

17. Process for the preparation of crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-

c]pyridine-5-yl)-acetate hydrochloride of the Formula I and hydrates thereof which comprises dissolving methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate in a dipolar aprotic solvent or a mixture thereof, admixing the solution with a solution of hydrogen chloride formed with an aprotic solvent or a mixture thereof and isolating the crystalline form II polymorph.

18. Process according to Claim 17 which comprises using acetone, acetonitrile, ethyl acetate or dimethyl formamide or a mixture thereof as aprotic solvent.

19. Process according to Claim 18 which comprises using a mixture of acetone and ethyl acetate as solvent.

20. Process according to any of Claims 17-19 which comprises carrying out salt formation at room temperature.

21. Pharmaceutical composition comprising as active ingredient crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula I or a hydrate thereof in admixture with inert solid or liquid pharmaceutical carriers and/or auxiliary agents.

22. Process for the preparation of pharmaceutical compositions according to Claim 21 which comprises admixing crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof with pharmaceutically acceptable solid or liquid carriers and/or auxiliary agents and bringing the mixture to a galenic form.

23. Crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof for use as pharmaceutical active ingredient.

24. Use of crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof as pharmaceutical active ingredient having blood platelet aggregation inhibiting and antithrombotic effect.

25. Blood platelet aggregation inhibiting and antithrombotic method of treatment which comprises administering to the patient in need of such treatment a therapeutically effective amount of crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof.

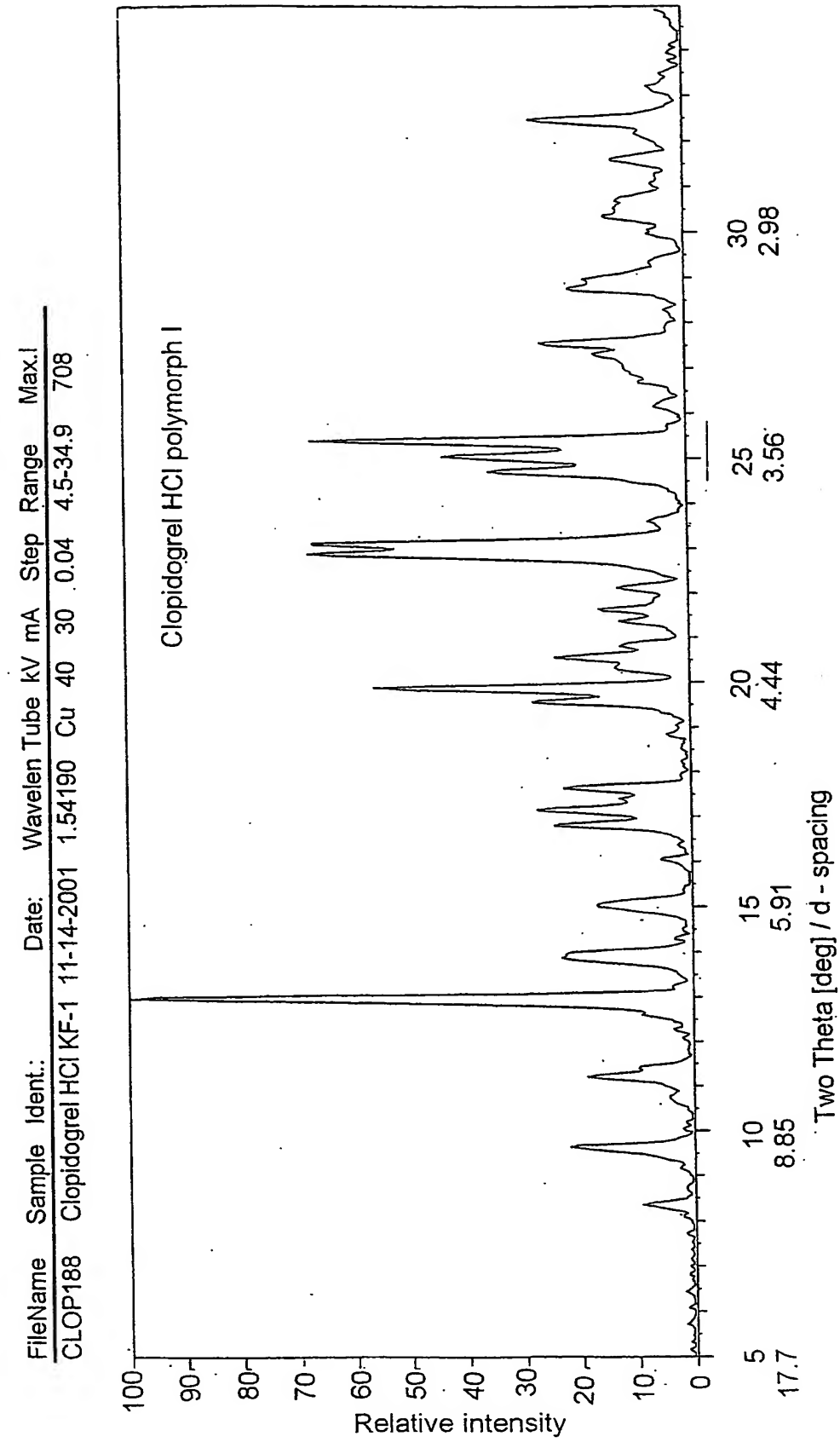

FileName Sample Ident.: Date: Wavelen Tube kV mA Step Range Max.I
CLOP188 Clopidogrel HCl KF-1 11-14-2001 1.54190 Cu 40 30 0.04 4.5-34.9 708
Clopidogrel HCl polymorph I
Relative intensity
100
90
80
70
60
50
40
30
20
10
0
5 10 15 20 25 30
17.7 8.85 5.91 4.44 3.56 2.98
Two Theta [deg] / d - spacing

Figure 1

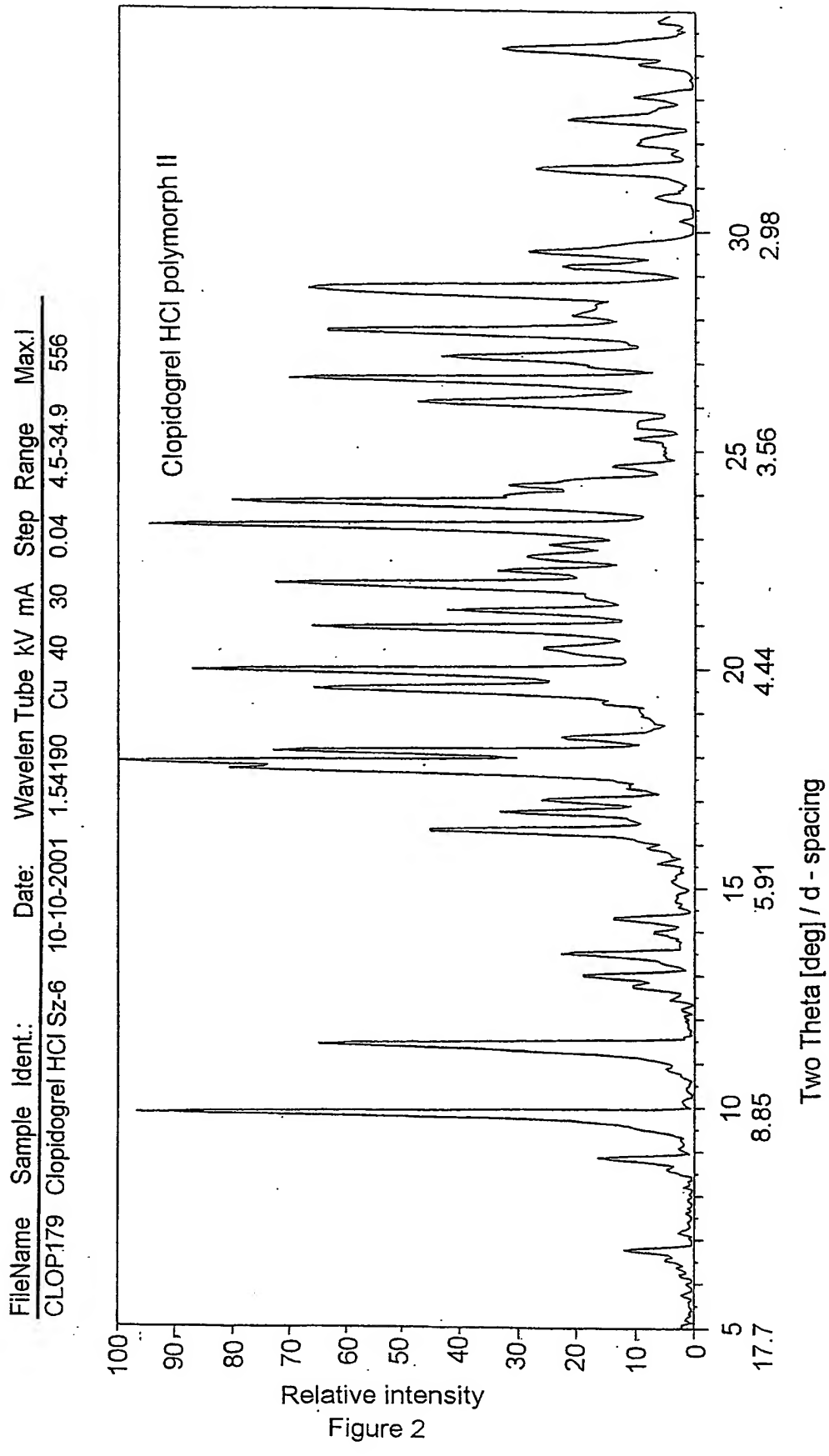

FileName Sample Ident.: Date: Wavelen Tube kV mA Step Range Max.I
CLOP179 Clopidogrel HCl Sz-6 10-10-2001 1.54190 Cu 40 30 0.04 4.5-34.9 556
Clopidogrel HCl polymorph II
Relative intensity
100
90
80
70
60
50
40
30
20
10
0
5 10 15 20 25 30
17.7 8.85 5.91 4.44 3.56 2.98
Two Theta [deg] / d - spacing

Figure 2

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/HU 02/00157

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D495/04 A61K31/4365 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 099 802 A (SANOFI SA) 1 February 1984 (1984-02-01) claims 1,14	1-25
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 March 2003	18/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Samsam Bakhtiary, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int[illegible]nal Application No
PCT/HU 02/00157

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HERBERT J-M: "CLOPIDOGREL AND ANTIPLATELET THERAPY" EXPERT OPINION ON INVESTIGATIONAL DRUGS, ASHLEY PUBLICATIONS LTD., LONDON, GB, vol. 3, no. 5, 1 May 1994 (1994-05-01), pages 449-455, XP000607616 ISSN: 1354-3784 the whole document	1-25

INTERNATIONAL SEARCH REPORT

ıational application No.
PCT/HU 02/00157

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 25 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

formation on patent family members

Int[illegible]nal Application No
PCT/HU 02/00157

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INTERNATIONAL SEARCH REPORT

...formation on patent family members

Int nal Application No
PCT/HU 02/00157

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